What's new in IPF drugs?

Katy Black, MD

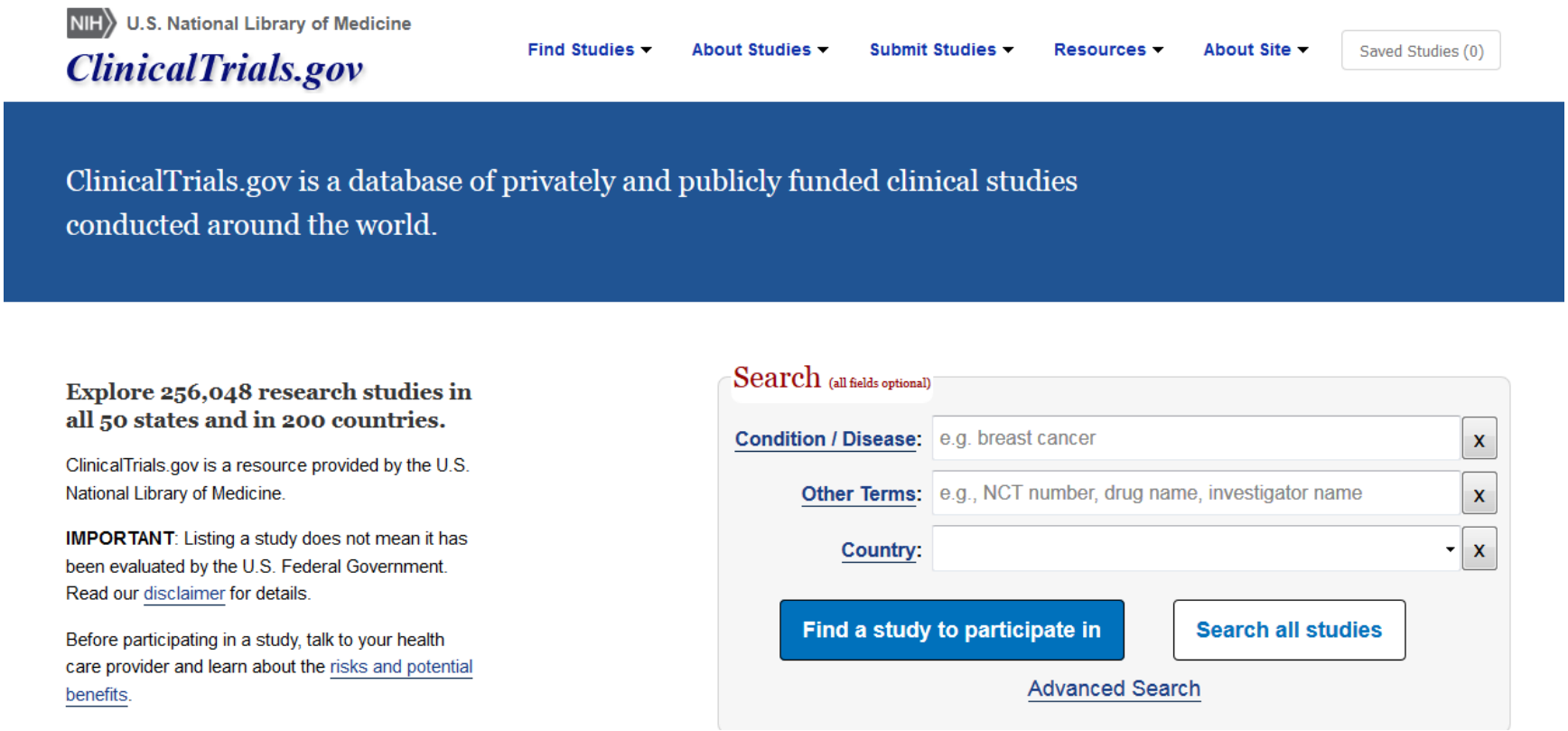
October 5, 2017

Clinical Trial terms

- Phase I: SAFETY (20-100 normal volunteer)
  - Focus on side effects and dosing
- Phase II: Disease specific
  - Focus on dosing and side effects in target population
    - 2a: is it doing what we think
    - 2b:what's the best dose
- Phase 3: EFFICACY (300-3,000)
  - Does it work?
  - Primary and secondary endpoints

https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

https://clinicaltrials.gov



Look for NCT number on all trials

A Phase 2 Study to Evaluate the Safety and Tolerability of PBI-4050 in Patients With Idiopathic Pulmonary Fibrosis (IPF)

This study has been completed.

Sponsor:
ProMetic BioSciences Inc.

ClinicalTrials.gov Identifier:
NCT02538536

First Posted: September 2, 2015
Last Update Posted: April 11, 2017

Note that anyone can register a trial, so being on the clinicaltrial.gov website doesn't prove it's legitimate!
Try to notice who is sponsoring the trial – academic center? Pharma company?
Will also list inclusion criteria: How old? What PFTs?

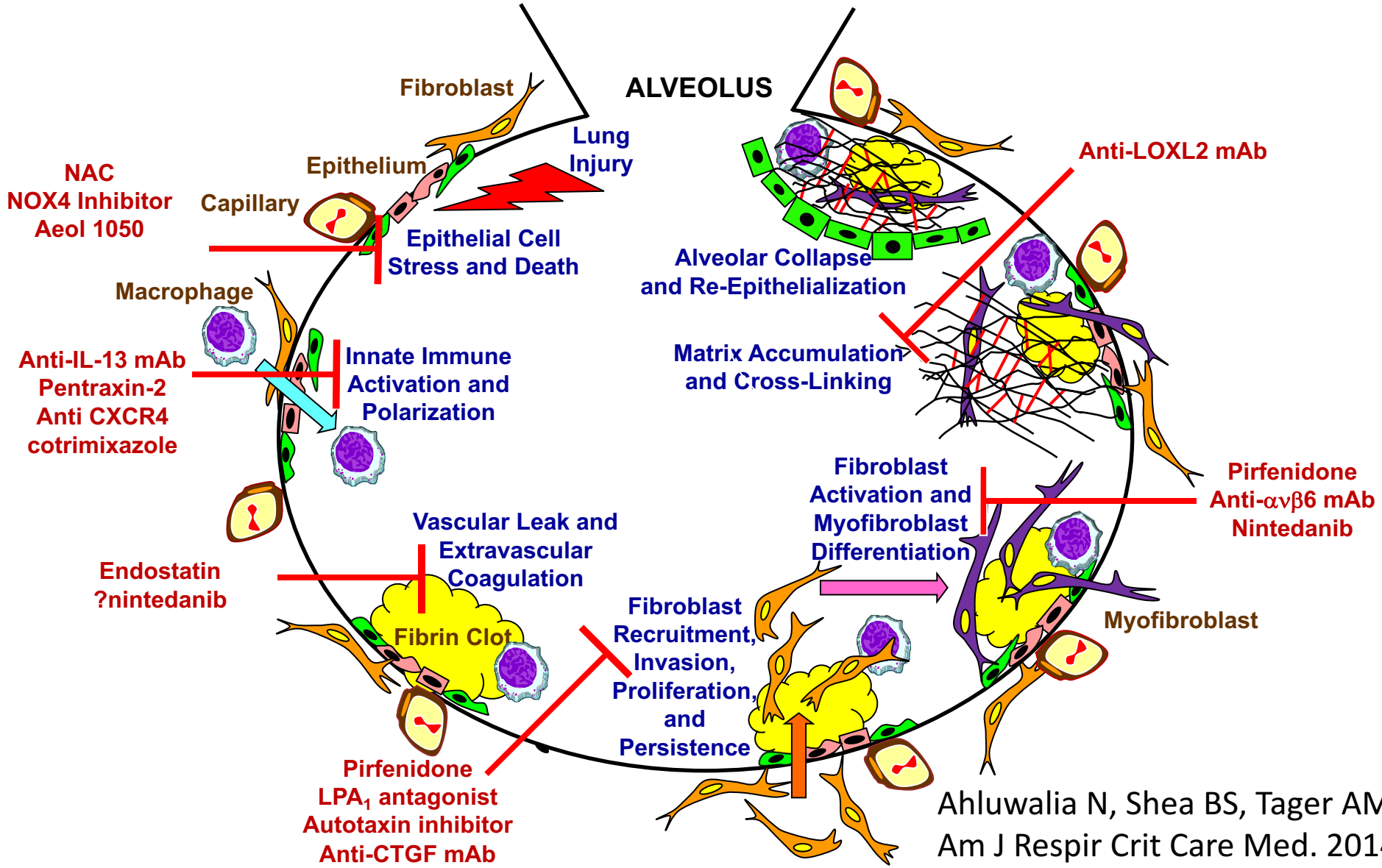
https://pulmonaryfibrosisnews.com/

- Treatment-> >experimental

PULMONARY FIBROSIS NEWS

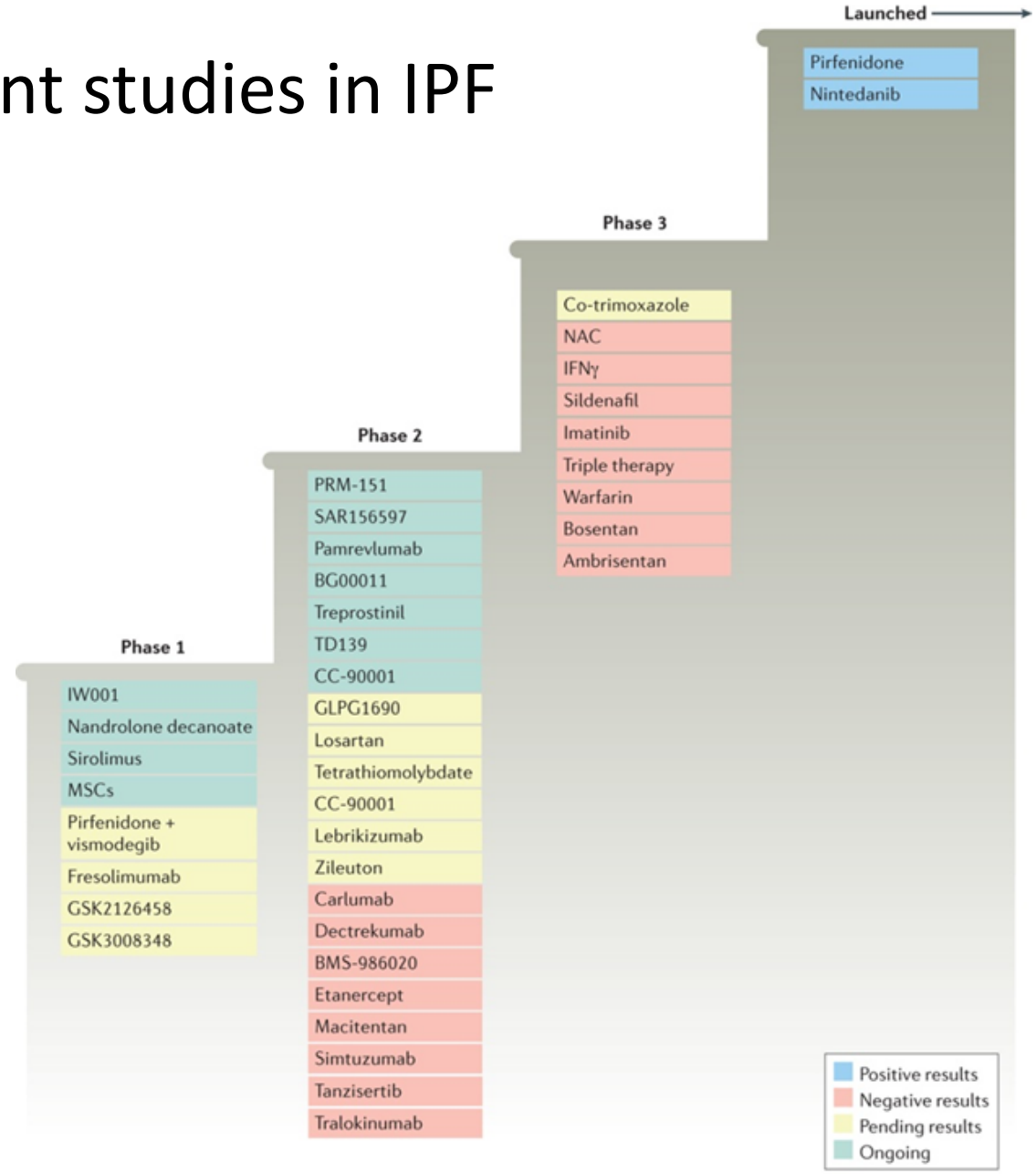
"News" from pharmaceutical – so being mentioned here does not imply endorsement from scientific community- but can find published references etc.

How can we cure IPF?



Ahluwalia N, Shea BS, Tager AM.
Am J Respir Crit Care Med. 2014

Review of recent studies in IPF



Mora..Selman
Nat Rev Drug Discov. 2017 Nov;16(11):755-772.

Take Home

- Lots of promising drugs in the pipeline
- Clinicaltrials.gov should list all potential trials and relevant details
  - Locations of study
  - Inclusion/exclusion
- Local research coordinators will help you look at real-world details
- If not registered with PFF registry and want to be, contact me! kblack1@partners.org

Specific drugs

- Loosely organized by the way the science suggests they would work
- Information from literature or the company's website
- No endorsement implied!

Targeting the scar

- BMS 986020
- GLPG1690

- FG-3019/pamrevlumab

- Simtuzumab

FG 3019- Pamrevlumab

Basic: Antibody to connective tissue growth factor (CTGF)

Science: CTGF activates fibroblasts

Prior studies: Phase I

Recent Phase II

- Pts 40-80 with IPF <6 years; FVC >-55%
- Outcome: change in % predicted FVC over 48 weeks
- Other outcomes: death, QOL, change in DLCO, hospitalization
- Company says results promising – stabilization, some improvement

NCT01890265 – sponsor = Pharma

FG 3019 : Pamrevlumab

- Substudy in patients on pirfenidone or nintedanib: “PRAISE” study
  - Reported at ERS conference this year
  - 2.85% decline in pamrevlumab vs 7% placebo
  - Now awaiting results in patients on active drugs

BMS 986020

- **Intro:** Lysophosphatidic Acid receptor 1 (LPA1) Antagonist
- Science: Discovered by Andy Tager to be critical in fibroblast movement and activation

BMS 986020

- Phase I completed in Jan
- Phase II completed Feb 2016

  included: IPF 40-90, no asthma, no improvement over 1 year

  Rate of change in forced vital capacity (FVC) over 26 weeks, HRCT changes 6mwt Time Frame

  Same drug had liver side effects in scleroderma, so stopped study

GLPG1690

- Intro: inhibits the enzyme “autotaxin” which makes LPA
- Science: Blocking autotaxin mean less LPA to activate fibroblasts
- Data: some efficacy in mice
  - (conflicting data using with other autotaxin inhibitors in mice)

Desroy J. Med. Chem., 2017, 60 (9), pp 3580–3590
Black FASEB J. 2016 Jun;30(6):2435-50.

GLPG1690

- Phase I completed 2015
- Phase IIa Study: FLORA trial (3/16-5/17)
- 23 IPF patient (17 on drug, 6 on placebo)
- Primary outcome: safety
- According to press release; those on drug had stable FVC over 12 weeks (reported August 2017) (vs. down very slightly)

Simtuzumab GS-6624

- Intro: Humanized antibody against Lysl oxidase-like 2
- Science: LOXL2 stabilizes scar tissue in IPF, so blocking that should let scar get softer
- Data: Large randomized double blinded phase 2 study (272 pts each group; 183 locations); looked at survival and function
- Stopped early: No effect
- New drugs targeting same pathway being developed

Raghu Lancet Respir Med. 2017 Jan;5(1):22-32.

IW-001

- Intro: Oral Antibody to collagen V
- Science: normally collagen V is hidden from immune system, but in pulmonary fibrosis it is exposed and could trigger an immune response; turning that off could help
- Phase 1 in 30 IPF patients (with anti collagen antibodies completed 2012; published 2015

Wilkes Eur Respir J. 2015 May;45(5):1393-402.

Vitta lPLoS One. 2013; 8(10): e76451

NCT01199887

PBI-4050

- Intro “Antifibrotic”
- Science: Tested in mice for ability to reduce known profibrotic factors
- Phase II trial 40 pts across Canada – data presented at ATS 2017
- 9 PBI-4050 only, 15 nintedanib, 16 pirfenidone
  - Pirfenidone blocked absorption of PBI-4050
- Seemed to stabilize patients
- Planning Phase 2/3 trial soon

NCT02538536

Targeting immune system

- Lebrikizumab

- Cotrimoxazole
- Valgancylovir

Lebrikizumab

- Humanized antibody to IL-13
- Science: IL-13 is produced by some T cells of the immune system, and can activate fibroblasts and epithelial cells, so blocking IL-13 could help
- Trialed in asthma as well
- Phase II trial in IPF
  - IPF pts over 40+
  - Skin injections every 4 weeks +/- pirfenidone
  - Started Oct 2013; should be done Nov 15, 2017!

NCT01872689 Hoffmann-La Roche

Cotrimoxazole

- Trimethoprim 80 mg and sulfamethoxazole 400
- ("Bactrim")
- Science: infections might contribute to progression; changing "microbiome" may alter disease
- IPF patients have more bacteria in lavage fluid
- ? Role of organism called Pneumocystics jirovecii
- Prior double blind multicenter trial:
  - 181 pts Co-trimoxazole 960 mg (two 480 mg tablets) or bid

Molyneaux PL et al. Am J Respir Crit Care Med. 2014 Oct
SihulingaThorax. 2013 Feb;68(2):155-62

CleanUP IPF

Study of Co-trimoxazole or Doxycycline and their Impact on Clinical Outcomes Using Pragmatic Design in Idiopathic Pulmonary Fibrosis

Phase 3 trial

- Primary Outcome: time to respiratory hospitalization or death
  - Other hospitalization, changes in PFTs, # of infections, QOL
- Enrolling: IPF >=40, no recent antibiotics
- 160mg trimethoprim/800mg sulfamethoxazole (double strength twice daily plus folic acid 5 mg daily
- If allergic-> doxycycline

NCT02759120 – sponsored by Weill Medical College of Cornell University

Valganciclovir hydrochloride

- Antiviral drug that works against herpesviruses, CMV
- Science: these viruses mabe promoting diseases
- Phase 1b trial to begin at Vanderbilt
  - single-center, prospective, randomized, placebo-controlled, double-blind pilot study
  - Requires bronchoscopy to test infections

NCT02871401, Vanderbilt and Pharma

Preventing damage

- VAS 2870
- Aeol 10150
- PTL-202

VAS 2870

- Blocks NAD(P)H oxidases (Nox) that creates reactive oxygen species
- Science: Blocking Nox should lower amount of reactive oxygen and decrease fibrotic response
- Phase II trial of similar compound **GKT137831** tested in diabetes kidney disease
- No human data

Ten Freyhaus Cardiovasc Res. 2006 Jul 15;71(2):331-41.
.Hecker Cell Mol Life Sci. 2012 Jul; 69(14): 2365–2371.

Aeol 10150

Basics: metalloporphyrin antioxidant,

Like natural enzyme superoxide dismutase

Converts reactive oxygen (O2-) into H2O2

Science: oxidative damage to epithelial cells may drive IPF progression

Indications: Acute Radiation Sickness, nerve gas damage, IPF, cancer

Data so far:

Preclinical : tested in mice and macaques against radiation-induced pneumonitis

Clinical: Phase I trials (safety) completed (Sep 18 press release)

MacVittie et al. Radiation Research 187(3):298-318. 2017

Tipelukast- MN001

- Oral anti-inflammatory
- Tested for bladder irritation
- Now planning trial
- (also in bladder, liver disease

BJU Int. 2006 Aug;98(2):430-4.

PRM-151

- recombinant human serum amyloid P/ pentraxin 2 protein
- Science:
  - pentraxin may block activation of inflammatory cells
- Data:
  - Phase II trial published in March 2016
  - 21 pts, safe but not much effect.

NCT01254409, sponsor pharma.

Van dem Blink Eur Respir J. 2016 Mar;47(3):889-97

PTL-202

- Combination of pentoxyfilline and N-acetyl-cysteine – two approved drugs
- Phase I showed safe; easier to take (only 1/day)
- No efficacy data

New pathways

- PRM 151
- TD 139
- KD025

- RES-529

TD 139

- Intro: Inhaled inhibitor of galectin-3
- Science: Galectin-3 has been shown to be important in recruiting fibroblasts and activating macrophages
- Data: Mice
- Completed Phase 1-2 study in Dec 2016
- (required bronchoscopy to measure drug levels)

NCT02257177

KD025 SLX-2119

- Intro: blocks ROCK2
- Science: blocking signaling pathways might work
- Mouse models show effect

- Phase 2, open-label, 24-week study examines the
- IPF patients on pirfenidone and/or nintedanib.
- Thirty- six patients : 24 with KD025 at 400 mg QD, 12 patients treated with standard of care

NCT02688647 : Sponsor Pharma

RES-529

- Small molecule that blocks TORC1/TORC2 interaction
- Phase I for macular degneration
- Pre-clinical for glioblastioma
- Pre clinical data about myofibroblast activation

Fentanyl for shortness of breath

- Fentanyl – potent opiod
- Primary trial of inhaled fentanyl : dyspnea (in Ontario)
- Measure breathing

NCT03018756

iBio-CFB03

- Basic: Endostatin derived peptide
- Scienc:
  - Endostatin – fragment of a collagen subtype; blocks blood vessel growth
  - Endostatin-like peptides are grown in plants
- Data: mouse of scleroderma and IPF
  - (Dr. Carol Feghali-Bostwick)
- No human data; patent in June 2016

Yamaguchi Sci Transl Med. 2012 May 30; 4(1

AD-114

Basic idea: new kind of antibody to CXCR4

- CXC chemokine receptor family of GPCRs,
- ligand CXCL12 (also known as stromal cell-derived factor 1, SDF-1
- Receptor seems to have role in cancers, stabilizing stem cells
- Different antibody structure may bind better
  - variable new antigen receptors (V_{NAR}s) from shark!

- Prior data: No clinical data
  - Plans to be tested in multiple diseases

Griffiths et al. J Biol Chem. 2016 Jun 10; 291(24): 12641–12657.

Exacerbations

- New case report used nintedanib

ART-123

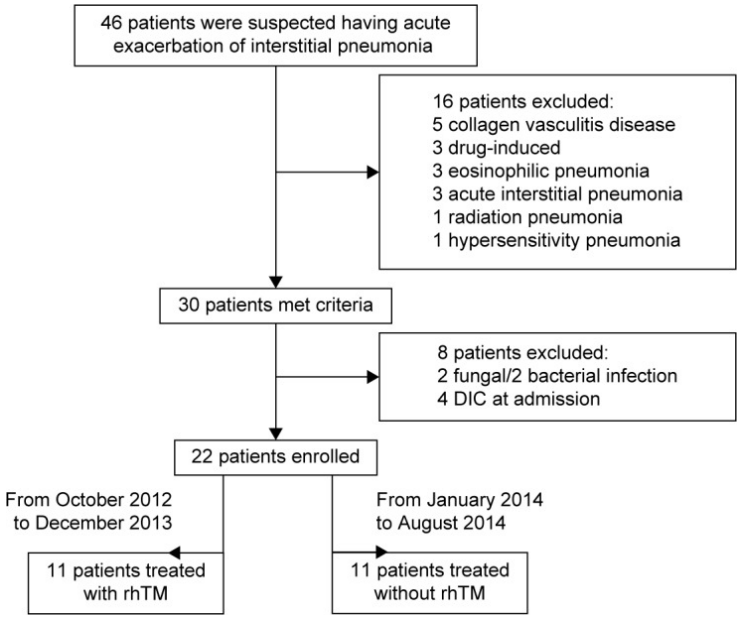
Underlying idea: human recombinant thrombomodulin

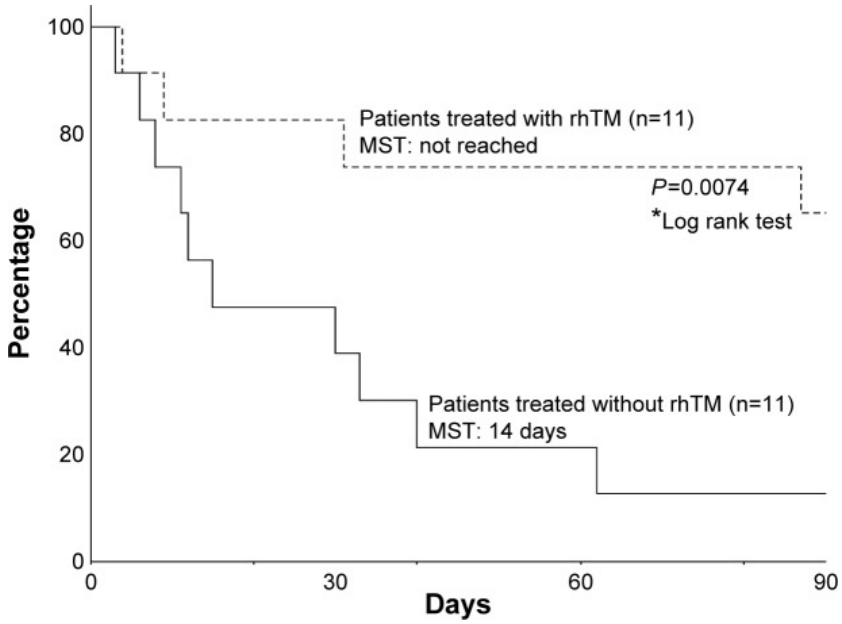
- Science:
  - anti clotting factor – accelerates thrombin's activation of protein- >turns off thrombin
  - Thrombin has other pro-fibrotic activity, so reducing it's activity has potential profibrotic effects
- Approved in 2008 in Japan for treatment of "Disseminated Intravascular Coagulation ("Recomodulin")

Drug Des Devel Ther. 2015; 9: 5755–5762.

ART-120

- Data so far: Prospective study – 22 patients
- Non randomized, single center
- 90 mortality: 36% vs 90%, *P*=0.023; median survival time: not reached vs 15.0 days, *P*=0.019)





Abe et al. Drug Des Devel Ther. 2015; 9: 5755–5762.

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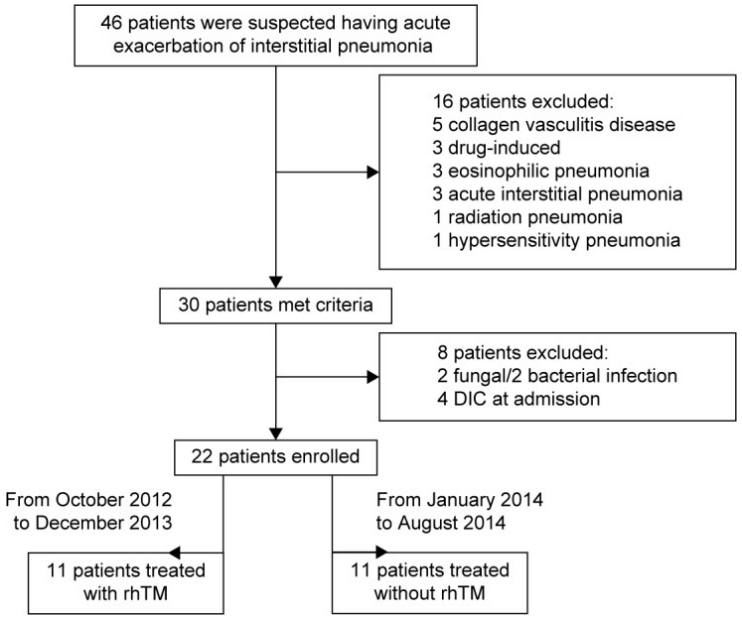

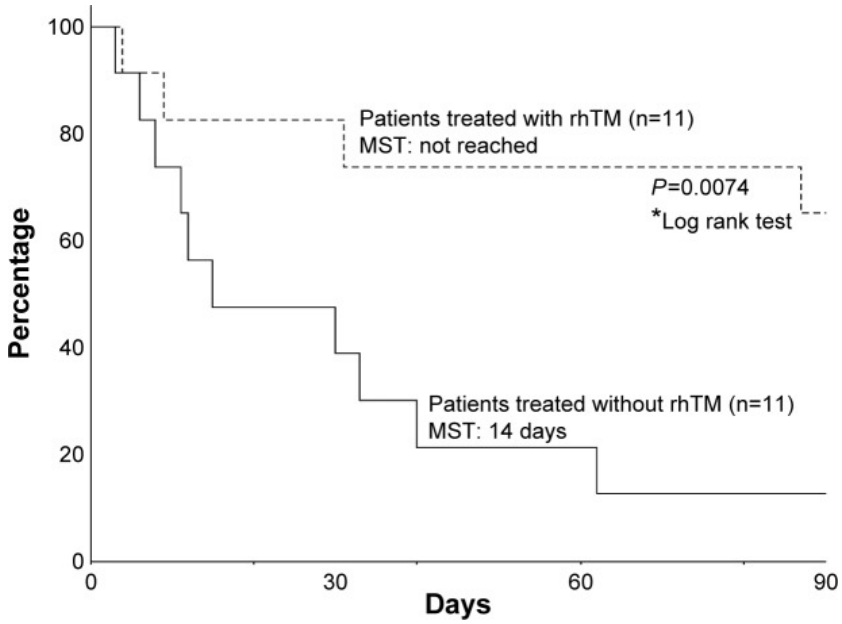

Abe et al. Drug Des Devel Ther. 2015; 9: 5755–5762.

Clinical Study of ART-123 for the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Ongoing trial in Japan

multicenter, double-blind, randomized, placebo-controlled, parallel group comparison study

Drug vs. placebo (+ standard of care)

Outcome: survival rate on Day 90 as the primary endpoint

Enrolling: IPF patients 40-80

Expected to complete: in July 2018

Sponsor: Pharma

Lots of reasons for hope!